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Original Articles

by

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1945

THE DIVERSE CLINICAL PICTURE OF CORONARY HEART DISEASE*

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WHEN, as the result of much study and discussion, the cardinal features of a clinical picture have been clearly defined, there comes a time when some of its less common aspects deserve mention. And often, after attention has been directed to these variants from the usual pattern, it appears that, after all, they are not such rare occurrences as was at first believed.

Coronary heart disease, in most cases the result of atherosclerosis of the coronary arteries, has indeed been a topic of widespread interest during the past quarter of a century. Its frequency has commanded respect. Many of its more dramatic symptoms are familiar not only to the physician but also to the well-informed layman. In stressing the diversity of its manifestations, I lay no claim to novelty. Examples such as those to be described and which serve as a basis for comment have, I am sure, been observed by many others.

In his book, titled "An Introduction to the Study of Physic," William Heberden,[1] better known for his classic description of angina

* Read at the Annual Meeting of The New York Academy of Medicine, January 4, 1945.

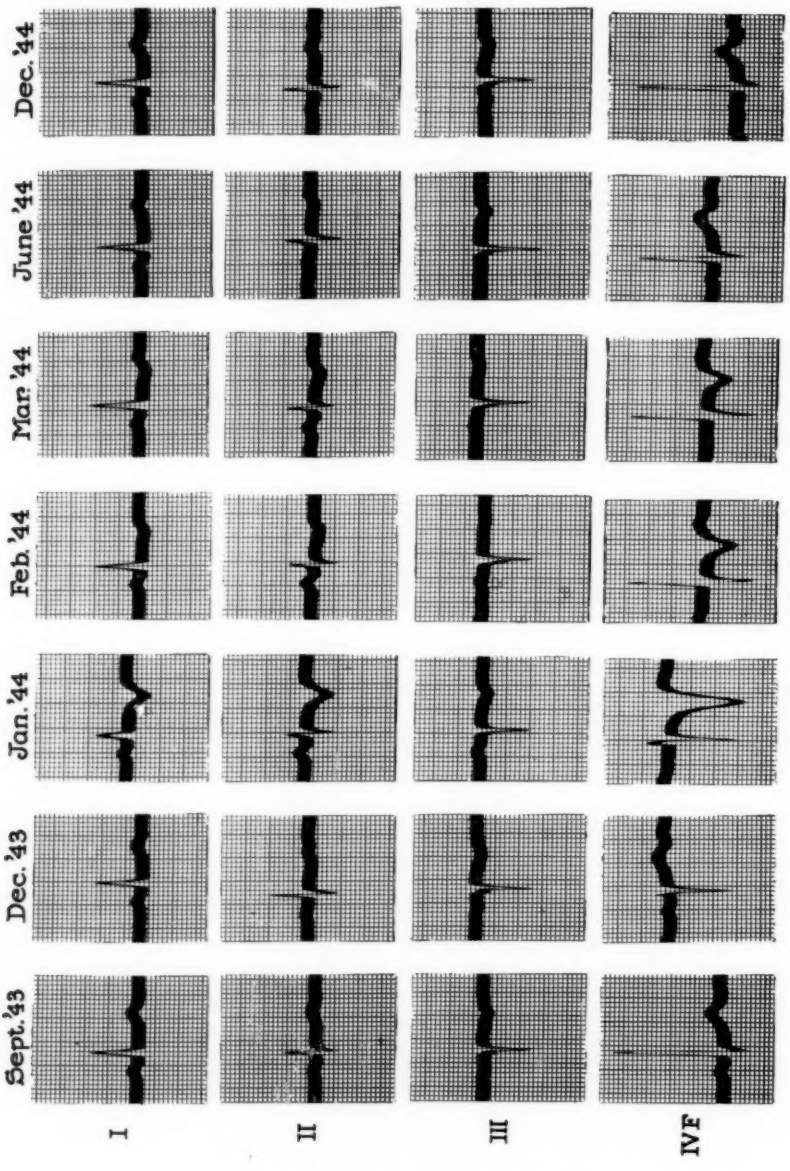

Fig. 1.-Case 1. Electrocardiograms of a woman, aged 71 years, with hypertension and mild symptoms. The alterations in the form of the complexes are striking.

pectoris, offers this suggestion: "Whoever would make a due use of his attendance on hospitals must be at the pains of writing down the history of diseases and the method of cure, that he may have a fair view of the case after it is ended, and to fix it deeper in his memory." It is with these simple aims in mind that the notes which follow have been compiled.

Case Reports and Comments

Case 1. Mrs. A. was first seen at the age of 67, four and a half years ago. She had been remarkably healthy and led a pleasant, comfortable existence. She had been aware of the presence of hypertension for eight years and for six months had noted palpitation when nervously upset.

Examination showed a small, slender woman with moderately marked retinal sclerosis. The heart was not enlarged. The sounds were of good quality and a faint systolic murmur was heard at the apex, as well as at the aortic area. The blood pressure was 198/102. There were no signs of congestive failure. The electrocardiogram showed left axis deviation, inversion of T 3, and an occasional auricular premature beat.

The patient fared remarkably well for a period of three and a half years during which the systolic pressure ranged from 212 to 174; the diastolic, from 104 to 74. She led a normal life, avoiding undue exertion and taking an adequate amount of rest. On December 2nd, 1943, she returned to New York after having spent two weeks in Boston where she attended an operation performed on her sister. Although not fatigued, she was aware of having gone through a trying experience. The blood pressure then was 206/96. The electrocardiogram, for the first time, showed slight changes; in Lead 2 the T wave was inverted and in Lead 4F, R was small and S deep.

On January 25th, 1944 (eight weeks later), she reported that she had been very tired after her Christmas shopping and had gone to bed for a week during which she had slight fever. She called a physician who thought she might have a cold, but the patient herself was sure that she did not. There was no pain in the chest; her chief complaint was that she felt completely "done in." She was told that during this episode her blood pressure fell to 170. Since that time, she had had a good deal of aching pain in the left arm which she thought was rheumatic.

The heart rate was 72; the rhythm was regular. The blood pressure

was 202/96. Measurement of the transverse diameter of the heart in the orthodiagram showed an increase of a full centimeter compared to what it had been on December 2nd, 1943. The electrocardiogram showed striking changes, with deep inversion of the T wave in all leads (Fig. 1). The leukocytes numbered 5,600, of which 62 per cent were polymorphonuclears. The sedimentation rate of the erythrocytes (Westergren method) was 15 mm. in one hour. She was sent home and placed under nursing care.

During the next three weeks she was kept in bed. There was no discomfort in the chest at any time, nor was there any elevation of temperature. The blood pressure was maintained at approximately the levels already noted. During the first few days, the cardiac rhythm was irregular due to premature contractions. At the end of four weeks she resumed her usual activities. There have been no further upsets.

There was a striking discrepancy between the mild symptomatology and the marked changes in the electrocardiograms. Regression of the deformities in the complexes was slow but complete; and about seven months after the short febrile illness, the record resumed its previous form.

Comment: In this case, the electrocardiographic changes suggested a wide area of cardiac involvement; yet discomfort was slight and the patient was ambulatory for at least three weeks before she thought it worth while to report for examination. It seems probable that one or more coronary branches became occluded without the formation of a large area of infarction. Healing apparently was excellent.

Inversion of the T wave in all of the three standard leads of the electrocardiogram is a relatively uncommon occurrence. It is observed most frequently after acute coronary occlusion but may be found in a variety of other cardiac disorders. A few instances have been noted in which there was no demonstrable heart disease. In sixteen cases with this electrocardiographic pattern and symptoms of hypertension and coronary insufficiency during life, the heart was examined at autopsy by Barnes and Burchell.[2] The usual findings were hypertrophy, severe coronary sclerosis and patchy fibrosis of the myocardium.

Case 2. Mr. B., a business man, aged 45 years, was first seen in July 1938, complaining of precordial pain and a heart murmur. Both were first noted two years previously. The pain was dull and often unrelated to exertion. There was no radiation to either arm.

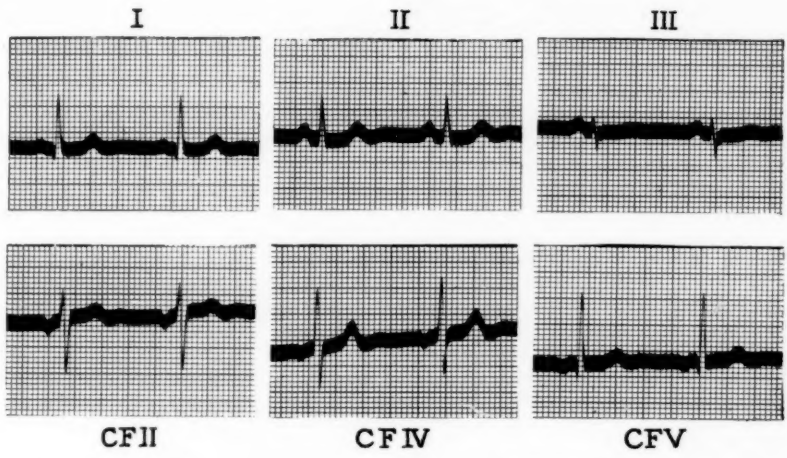

Fig. 2.-Case 2. Electrocardiogram of a man, aged 51 years. There is very slight concavity of the RS-T segments in Leads 1 and 2. Sudden death occurred one month later, as a result of fright.

Physical examination was negative. There was no retinal sclerosis. The heart sounds were clear. The blood pressure was 134/86. The electrocardiogram showed very slight concavity of the RS-T segments in Leads 1 and 2. He was obese and was advised to lose weight. He was asked to return if the symptoms persisted.

He was not seen again until October 11th, 1944, more than six years later. Apparently for two years after his first visit, he was quite well; then, four years ago, the pain returned with increasing severity and frequency. He could only walk one block without stopping to rest. Excitement at the race track caused the most intense discomfort. There was now radiation to the arms. He had not used nitroglycerin. Roentgenologic examination of the gall bladder, made several years previously, revealed sluggish emptying but no stones. He did not smoke and because liquor caused him to flush and made his heart beat rapidly, he took it rarely.

Examination showed a loss of sixteen pounds in weight in the past six years. The heart was not enlarged. The sounds were clear. The blood pressure was 128/84. The electrocardiogram showed left axis deviation and again, very slight concavity of the RS-T segments in Leads 1 and 2 (Fig. 2). The record was similar to the one taken at the time of his first visit.

It seemed clear that this man's discomfort was due to coronary insufficiency and a suitable regimen of activity and rest was outlined.

Exactly one month later, the patient's death was reported in the newspapers. His body, fully clothed, was found on his bed, where also lay his wife's jewel case. This had been forced open and several of the larger pieces of jewelry were missing. In the living room of the apartment, drawers of desks had been pulled out and the contents scattered about the room. The liquor cabinet had been opened and two bottles were lying on the floor. Chairs on the terrace had been overturned. According to the New York Times, while the police were trying to determine the facts, the detective captain in charge stated that "Mr. B. may have come home and seen a burglar or evidence of a burglary and probably suffered a heart attack." Apparently this is precisely what happened.

The essential findings at autopsy were supplied through the courtesy of Deputy Chief Medical Examiner B. M. Vance. There was no evidence of external violence. The heart was not enlarged. There was marked sclerosis of both coronary arteries with calcification and extreme narrowing of the main branches. The myocardium showed patches of fibrosis. There was neither recent thrombosis nor cardiac infarction.

Comment: This is an instance of acute, fatal coronary insufficiency in which sudden death followed an intense emotional experience.[3] The lack of important signs of coronary heart disease during life is noteworthy although the symptoms were characteristic. This man literally was "scared to death."

Case 3. Mr. C., age 73, gave a story of substernal pain for three years. This occurred on walking in the wind or after a meal and disappeared promptly on standing still. He had never taken nitroglycerin for relief. One week before his visit, after breakfast, he had a more severe pain than usual which persisted for about two hours. There was no radiation to the arms. On the morning of his visit, he had a similar pain, also lasting for several hours; this had not entirely disappeared when he presented himself for examination.

There was slight retinal sclerosis. The heart was normal in size on percussion. The sounds were distant and the first sound at the apex was reduplicated. The blood pressure was 126/68, which he stated was his usual level. Fluoroscopic examination and an orthodiagraphic

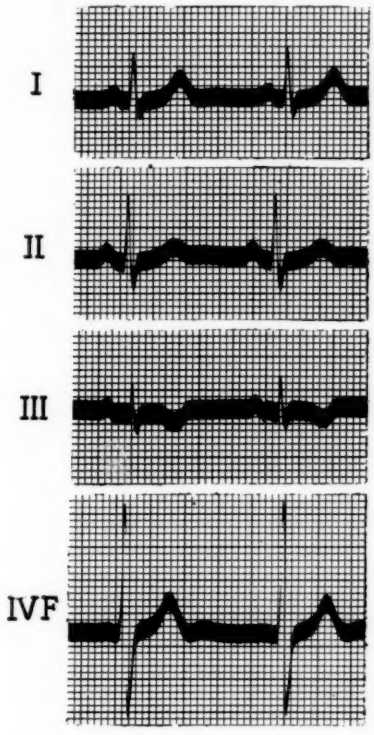

Fig. 3.-Case 3. Electrocardiogram of a man, aged 73 years. The record is within the range of normal. He died twenty-three hours later of acute coronary occlusion.

tracing showed no cardiac enlargement but the left ventricle was full and rounded. The electrocardiogram (Fig. 3) showed no significant changes. The erythrocyte sedimentation rate was 13 mm. in one hour (Westergren method).

The patient was advised to go home to bed. He felt so well that he walked several blocks to a druggist's shop to fill a prescription.

After a comfortable night, the pain recurred at noon on the next day. It was persistent and increased in severity. A state of shock soon developed and he died two hours later and twenty-three hours after the electrocardiogram was taken. Although an autopsy was not performed, it seemed clear that occlusion of a large coronary branch was responsible for the terminal episode.

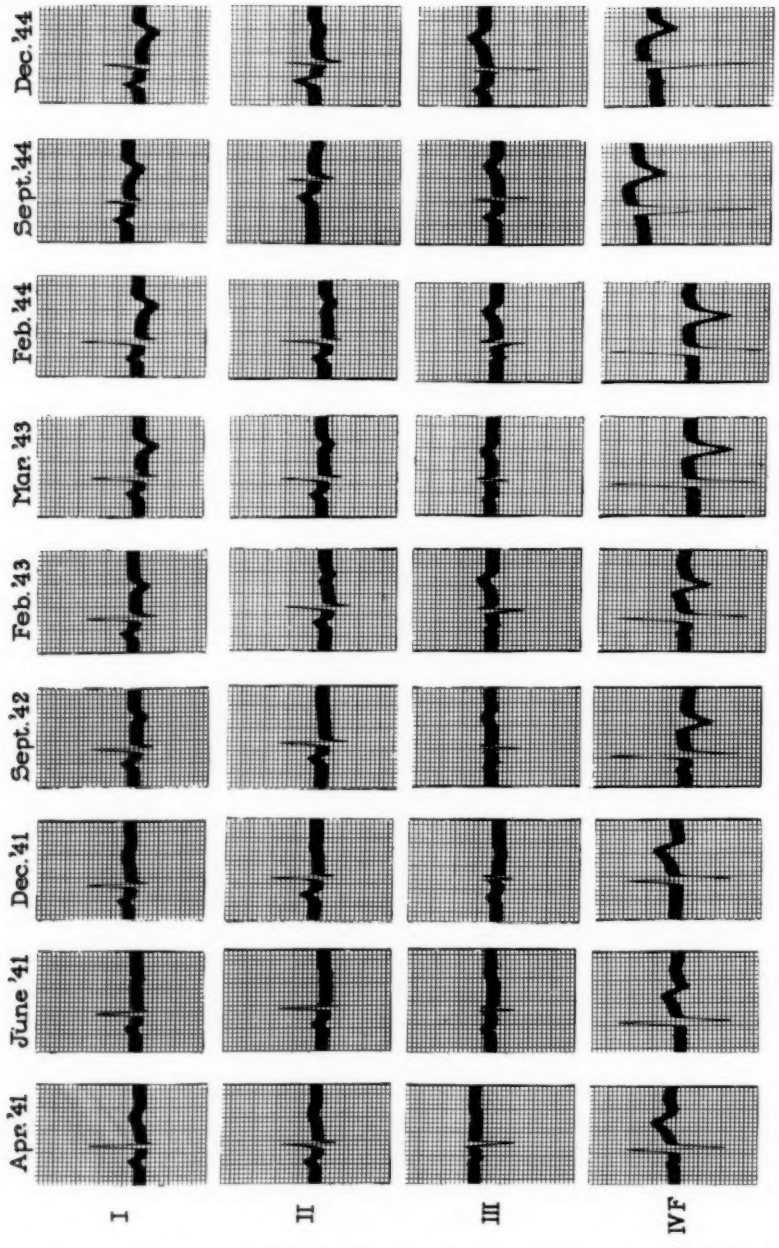

Fig. 4.-Case 4. Series of electrocardiograms of a man, aged 60 years when first seen. There are frequent and marked changes in form; but throughout this period of three and a half years, he has been active and entirely free from discomfort.

Comment: In this case, it is probable that actively progressive changes were taking place in a coronary artery for at least a week. In spite of this fact the electrocardiogram, taken less than twenty-four hours before death, afforded no clue to the impending closure.

Case 4. Mr. D., a lawyer, was first seen at the age of 60 in March 1941. There were no symptoms referable to the heart. He had recently been in a hospital for hemorrhoidectomy and at that time, an elevation of blood pressure was first noted. For this reason, he was referred for more complete examination.

There was moderate retinal sclerosis. The heart rate was 76; the rhythm was regular. The sounds were strong and clear. The blood pressure was 182/106. The electrocardiogram showed slight left axis deviation but was otherwise not remarkable. Measurement of the orthodiagram showed enlargement of the heart, chiefly to the left, and moderate, diffuse dilatation of the aorta.

The patient was seen at frequent intervals during the next three and a half years. He never had discomfort of any sort. He continued as a practising lawyer but shortened his hours of work and rested for an hour each day after lunch. He played golf regularly, both at home in the summer and in Florida in the winter. He danced moderately. In June 1944, he recovered from an attack of primary atypical pneumonia without any cardiac disturbance.

The series of electrocardiograms pictured in Fig. 4, shows changes which, taken by themselves, would lead to the belief that lesions of serious consequence had occurred in the heart. Certainly there were occlusions in the coronary bed; but these apparently developed gradually and in the presence of an adequate collateral circulation. At no time was there an increase in the sedimentation rate of the erythrocytes or any fall in blood pressure.

This patient was last seen on December 12th, 1944. He considered himself unusually well. The first sound at the apex was reduplicated and was followed by a short systolic murmur. The blood pressure was 164/114. The size of the heart was the same as in March 1941.

Comment: These striking electrocardiographic changes occurred in an elderly man with hypertension who, throughout the period of over three years during which they were observed, led an active professional life, danced and played golf. He was entirely free from discomfort. I confess that at times I was somewhat concerned about the wisdom of

sanctioning this regimen. Yet there did not seem to be sufficient reason to advise that he relinquish the interests and relaxations which he enjoyed; and I know that he preferred to assume whatever risk was involved rather than to live on a lower plane of activity. It is questionable whether he would now be any better off had he retired and rested; I doubt it. How long such a series of insults may be continued without symptomatic evidence of cardiac damage, will depend upon the balance between the amount of obstruction and the extent of the collaterals in the coronary bed.

If electrocardiograms are taken at frequent intervals in patients with coronary sclerosis, it is not uncommon to discover varying patterns without associated symptoms. Such an occurrence need not occasion surprise, for it is in accord with the concept that arterial degeneration is inherently a progressive process. The changes are not always as marked as in this case. But even several main coronary arteries may be occluded before the final illness, in the absence of anginal pain or congestive failure. This has been clearly demonstrated by Blumgart and his associates,[4] who correlated the clinical manifestations with the pathologic lesions in hearts injected and dissected at autopsy.

Case 5. Mr. E. was a manufacturer, 59 years of age. He complained of substernal pain. One brother died at 69 of cardiac disease; and one sister, who was living at the age of 71, had suffered from an attack of coronary thrombosis eighteen months previously. The patient had been treated for peptic ulcer nine years earlier, with relief of symptoms and apparent healing of the ulcer. Twenty months before I saw him, he had a tarry stool which was ascribed to bleeding from a small erosion of the gastric mucosa. This had healed.

The present discomfort began six weeks before his visit, with substernal pressure which occurred chiefly at night. Four weeks before, while playing cards, he first felt severe pain, lasting five minutes, and that same night, had further discomfort lasting a half hour. He was put to bed for four days and remained at home for a week following. There was some improvement but he still complained of nocturnal and early morning discomfort. Nitroglycerin gave prompt relief. There was no radiation of the pain but he experienced tingling in the left arm with the sharper attacks. He rarely smoked and drank liquor infrequently. He had continued at his business.

Examination showed well marked retinal sclerosis. The heart was

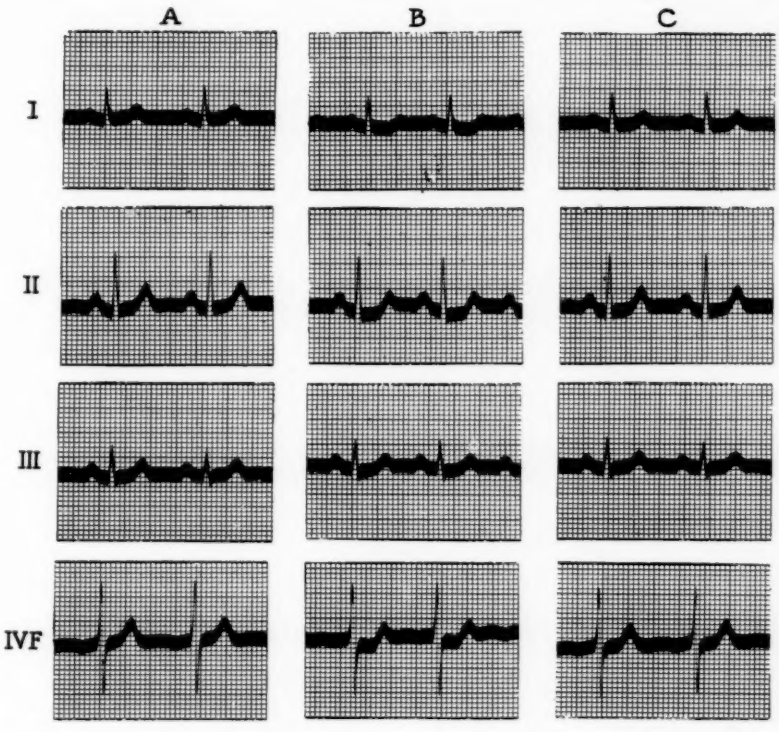

Fig. 5.-Case 5. Anoxemia test of a man, aged 59 years, with pain in the chest and a peptic ulcer. A, control. B, after breathing 10 per cent oxygen for twenty minutes. C, after breathing 100 per cent oxygen for two minutes. The test is positive. Depression of the RS-T segments, apparent in B, disappears promptly after inhalation of pure oxygen.

not enlarged, either on percussion or on roentgenologic examination. The rhythm was regular; the rate was 80. The sounds were moderate and no gallop was heard. There was a faint systolic murmur at the apex. The blood pressure was 144/78. The electrocardiogram was normal and was similar to those previously taken over a period of years.

In spite of the absence of clinical signs of coronary heart disease, it seemed probable that the patient's pain was due to coronary insufficiency. Because of his gastric history, it was suggested that roentgenologic examination of the gastro-intestinal tract be repeated. This was done and an active duodenal ulcer was found. There was no hiatus hernia. The consulting gastro-enterologist was of the opinion that dis-

comfort could be explained on the basis of the lesion in the digestive tract.

The patient's physician, however, was not satisfied with this interpretation and at his suggestion, Mr. E. returned for an anoxemia test. This was positive, as shown in Fig. 5. The changes were particularly evident in the RS-T segments. The sum of the deviations in the four leads totalled 3 mm. According to the criteria now employed, this is a sign of a positive test and indicates coronary insufficiency. The patient was able to breathe the 10 per cent oxygen mixture for twenty minutes but complained of slight substernal pressure during the last two minutes of the test. After breathing 100 per cent oxygen for two minutes, the changes in the electrocardiogram caused by anoxia were abolished.

Comment: The clinical picture in this case was confused by the presence of a peptic ulcer and the absence of definite signs of coronary heart disease. The anoxemia test afforded graphic evidence of coronary insufficiency.

The Anoxemia Test in Diagnosis

Not infrequently it is difficult to determine the source of discomfort in the chest, particularly when the patient complains of pain. Such discomfort may be due to various causes originating at a distance from the point of reference. Among conditions which sometimes cause confusion are gall stones, hiatus hernia, esophageal spasm, arthritis of the spine and a psychoneurotic state. Several procedures have been suggested to increase the work of the heart under conditions which make it possible to determine, indirectly, a diminution in coronary reserve. In the Department of Cardiology at the Presbyterian Hospital, we have been particularly concerned with the development of the anoxemia test.[5, 6]

This consists of permitting the patient to breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or until cardiac pain appears. A control electrocardiogram is taken and records are made at intervals of five minutes while the patient breathes the low oxygen mixture. Measurement of these records shows, in patients with a diminished coronary reserve, characteristic changes which are not observed when the coronary blood flow is adequate. Based on analysis of a large experience, criteria have been evolved which are regarded as evidence of a positive test.[7] The result is positive when any one of the

following is found:

1. The arithmetic sum of the RS-T deviations in the four leads employed (1, 2, 3 and 4F) totals 3 mm. or more.

2. There is partial or complete reversal of the T wave in Lead 1, accompanied by an RS-T deviation of 1 mm. or more in this lead.

3. There is complete reversal of the direction of the T wave in Lead 4F, regardless of any associated RS-T deviation in this lead.

The occurrence of pain during a test which is electrocardiographically negative is considered *presumptive* evidence of coronary insufficiency. In this event, the patient should be carefully watched for further signs of coronary disease and managed conservatively. Often such signs later make their appearance; and frequently the anoxemia test subsequently yields a positive result.

If carried out according to directions, the test is simple and safe. It has been found useful in differential diagnosis, both in our experience and that of others.[8,9] If three fundamental precautions are observed, serious reactions are avoided. The test should not be performed under the following circumstances: (1) in the presence of congestive heart failure; (2) within four months after known cardiac infarction; (3) on the same patient more than once in twenty-four hours. A positive test indicates a diminished coronary reserve but gives no information as to the nature and extent of the pathologic lesions in the heart. A negative result does not rule out the presence of disease of the coronary arteries; for, as in any functional test, there must be a significant decrease in reserve before insufficiency can be demonstrated.

Summary

Attention has been directed to some of the less common clinical aspects of coronary heart disease. There may be minimal symptoms and marked changes in the form of the electrocardiogram. In the presence of advanced coronary sclerosis, a severe emotional strain can induce acute coronary insufficiency and so cause sudden death. The electrocardiogram may be normal less than twenty-four hours before fatal coronary occlusion. There may be striking serial changes in the electrocardiogram, indicating closure of coronary arteries in a patient who is ambulatory, active and entirely free from cardiac discomfort. When the symptoms are puzzling and the examination, including the electrocardiogram, reveals no signs of heart disease, the anoxemia test is often useful in affording graphic evidence of a diminished coronary reserve.

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THE TREATMENT OF CORONARY DISEASE*

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IT WAS with reluctance and misgiving that I accepted the flattering invitation of your Committee to discuss the treatment of coronary disease. We all know that progress in this field, despite much hard work, has been modest and that we have little more than a toe-hold on the problems which beset us. Moreover the therapy of coronary disease has been discussed so frequently that one hesitates to add still another presentation to a literature whose volume is already out of proportion to knowledge of the subject. I could not cover all aspects of the topic assigned me in a presentation of this length. I have no startling new facts to bring to your attention. At most I can share with you certain of my reflections and points of view that have developed in the course of struggling with this problem for many years.

INVESTIGATIVE STANDARDS AND OBJECTIVES

The charge that its investigative work is not on a high plane has frequently been leveled against clinical medicine. The most recent of such criticisms to come to my attention is contained in the following quotation from Sir Thomas Lewis:[1] "Clearly to recognize the limitations of present day knowledge and fully to realize the contrast between medical writings and the closely reasoned argument and precise recording now found in the ancillary sciences, are matters of prime consequence in an approach to the problem of reform in medical education." One need not necessarily be so impressed as is Sir Thomas by the contrast between "medical writings" and those of the "ancillary sciences" but the need for closely reasoned argument and precise recording in all scientific fields can scarcely be challenged. One might add that the closely reasoned argument requires tests of the assumptions upon which

* From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.
Read January 4, 1945 at the Annual Meeting of The New York Academy of Medicine.

it is based as well as careful checking at every step by precise recording, otherwise, even those working in the ancillary sciences such as the physiologists may stray from the path of truth. I venture to assert that there are many clinical investigators whose work is fully up to the standard of the best produced by their confreres in physiology. On the other hand we have to admit that much of what is published in the clinical journals and books does not stem from that vitally essential combination of closely reasoned argument and precise recording. Too much of the literature dealing with coronary disease is open to this criticism, so much in fact that it constitutes a handicap to those trying to educate themselves and a burden to all who wish to keep abreast of current developments.

Advances in the treatment of coronary disease may result from the discovery of new and more effective procedures or from careful studies which demonstrate more clearly the indications and best methods of use of measures now available. The most urgent needs however are (1) improvement in diagnostic methods so that we can recognize the disease in a far earlier stage than at present and (2) more accurate and complete knowledge of the etiological factors concerned in its production.

The Unsatisfactory Status of Etiology

The difficulties which beset investigation of the causes of coronary disease could scarcely be overestimated. Because in the vast majority of cases it is a manifestation of atherosclerosis, it has been widely assumed that its causes are identical with those of atherosclerosis of other vessels. Such an assumption seems reasonable but it does not take into account possible causes of relatively early and extensive involvement of coronary arteries, as compared with certain other parts of the arterial tree, observed in some individuals. Experimental work seems to show that by certain procedures the coronary arteries can be acutely damaged without material involvement of other arteries.[2] Such results make it seem not unreasonable to entertain the idea that in humans certain etiological factors may produce selectively more atherosclerosis of coronary arteries than of other vessels. Dock[3] has suggested that their relatively thick intima may make these arteries vulnerable.

It seems to be assumed by most writers on the subject of coronary disease that not only is its incidence on the increase but that certain disorders dependent upon it such as angina pectoris and acute coronary

occlusion are increasing even more rapidly. Unfortunately we lack the "precise recording" by which such questions can be settled. Cohn and Lingg[4] in 1934 could not obtain evidence from comparative studies of vital statistics to indicate that coronary disease, taking into account "fashions in diagnosis" and lessened mortality in youth, was much more common than it had been thirty years before. There is no yardstick by which the comparative frequency of angina pectoris and acute coronary occlusion can be measured. One is impelled almost irresistibly to the conclusion that these conditions are more common to-day than they were in the past but evidence to establish that view is lacking. Although most of us knew nothing about acute coronary occlusion thirty years ago, the newspapers of that day featured the sudden death of prominent members of the community just about as frequently as they do now. I still recall the statement of the late Edward Martin made to his class in surgery in 1910 that nearly all of the sudden deaths reported in the newspapers as acute indigestion were in reality due to heart disease.

It would be very helpful if we could settle the question of the relative frequency of coronary disease or any of its manifestations today and in the past. If long familiarity with the assumption that they are increasing and frequent assertion of it make us believe that assumption to be established and we base further work on such a belief without holding it under question, we depart from the scientific method. Acceptance of untested but frequently repeated assumptions is undoubtedly one of the major causes of error in human reasoning. As one examines the upper range of the scale of intellectual sophistication, the traps for the unwary merely become harder to detect. The literature of medicine abounds with them even today. A classical example which does not leave untouched some of our colleagues in the "ancillary sciences" is the history of the Einthoven equilateral triangle hypothesis. This hypothesis constructed by erecting assumption upon assumption without testing most of them, has been used for over thirty years as the starting point for further research leading to voluminous literature. If even one of the important assumptions which underlie the famous hypothesis is shown to be invalid, as I believe it has been, this enormous superstructure falls like a house of cards and thirty years of work along certain lines will have proven a total loss. In view of the many untested assumptions regarding the causes of coronary disease which receive widespread acceptance I believe we are in danger of perpetuating major error in our

thinking and in our work on that subject and above all in our management of patients.

I shall offer only one illustration of the point I have tried to make above and select it because of its bearing on treatment. Many, including myself, believe that certain manifestations of coronary disease such as angina pectoris and acute coronary occlusion are much more common at relatively early ages in heavy smokers than in the general population. One can scarcely fail to be impressed by the large proportion of patients under the age of forty with such disorders who smoke cigars or cigarettes in great excess.[5] It is therefore tempting to conclude that tobacco has been responsible for the coronary disease and its consequences found in these relatively youthful patients. Moreover such a view is supported by other facts. The effect of tobacco in producing vasospasm in peripheral vessels has been demonstrated. Changes in the electrocardiogram can sometimes be produced and occasionally anginal attacks can be precipitated by smoking one or two cigarettes. The frequency of anginal attacks sometimes seems to be lessened if the use of tobacco is stopped. Such an array of evidence seems convincing. On the other hand, there are many heavy smokers who never develop any evidences of coronary disease, probably a far larger group than those who do. There are many other heavy smokers with angina pectoris who are not improved to any perceptible extent by stopping the use of tobacco. Finally one must ask himself to what extent it may be the restlessness, lack of self-discipline or whatever it is that makes some individuals heavy smokers, that is responsible for the coronary disease rather than the tobacco itself. Should we then on the basis of such an unproven case try to stop our patients with coronary disease from smoking? It is asking a lot of a man who is restricted in so many other ways to give up the solace of tobacco. It would seem unwise, however, to advise patients with frequently recurring anginal attacks to continue the use of tobacco without giving abstinence from it a fair trial, whether or not its use accelerates the progress of pathological changes in their arteries. In general it has seemed to me that patients with coronary disease who stop smoking do better than their less coöperative friends but perhaps this is because they follow all their orders better. We still have before us the task of proving that the use of tobacco tends to bring on coronary disease or shortens the life of its victims.

It may be found some day that there is one vital essential link in

the chain of developments leading to the production of atherosclerosis, just as has proved to be the case in the formerly equally mysterious pernicious anemia. In the latter the discovery of effective treatment antedated knowledge of etiology of the disease and actually led to it. However, pending such a happy development in the case of coronary disease we may attempt in so far as it is possible with our limited knowledge to utilize the method of multiple working hypotheses, assuming in each case the probability that a number of factors are operating more or less concurrently.

In view of the frequency of coronary disease and our inability to recognize it until it reaches an advanced stage in at least one or more places in the coronary arterial tree, I think we should assume that any man approaching the age of fifty may have the beginnings of coronary disease, no matter how healthy and vigorous he appears to be. Thus, when a presumably healthy individual of middle age or beyond asks what he can do to keep from getting heart disease, one can at least advise him to be moderate in all things. Obviously if there is a family tendency toward conditions known to accelerate the development of atherosclerosis such as diabetes or hypertension, special emphasis should be placed on examinations for such conditions in order to discover them in an early stage.

Periodic or Health Examinations

The rapidly increasing emphasis on preventive medicine and growing acceptance of periodic or health examinations by industrial organizations and by individuals present an ever greater problem to physicians concerned with the cardiovascular aspects of these examinations. Some papers advocating such examinations overestimate the ability of physicians to detect coronary disease in its early stages and to retard its further development. Too many who have been slapped heartily on the back and told they have no heart disease have died during the next few days or weeks, to the discredit of their optimistic examiners. The most one is justified in saying after a negative examination is that no evidence of heart disease has been found. On the other hand too many are told that they have heart disease on the basis of findings that do not actually establish the fact. In the past such a finding was often an innocent murmur; now it is apt to be some deviation from empirically derived electrocardiographic standards which do not deserve all the faith sometimes

reposed in them. The greatest problem of all concerns the far from small percentage of individuals in older age ranges who present unmistakable evidence of myocardial involvement, in some the result of hypertension but in many others coronary disease without hypertension. Perhaps the greatest single mistake made in the management of these groups is to assume that prognostic data obtained from the study of patients who seek medical advice because of illness apply with equal force to those who are without symptoms. For example bundle branch block in hospital practice has in general an ominous prognosis although there are many exceptions to the rule. On the other hand bundle branch block found in examinations of the presumably healthy has a far more favorable outlook. These individuals as well as others found to have evidence of coronary disease should be instructed to avoid strenuous physical activity, to obtain adequate rest and sleep and avoid indiscretions of food intake and intemperance in other habits. Those whose duties entail severe physical or mental strain should be advised to try to obtain easier work. However, care should be exercised not to place unnecessary restrictions on the lives of these men, and above all not to stop them from useful work if they are able to carry on, and wish to do so. Otherwise one may engender a sense of defeat, mental depression or anxiety. Individuals unnecessarily restricted like those who receive a mistaken diagnosis of heart disease would have been far better off without health examinations.

General Considerations in the Treatment of Patients

The evaluation of treatment in coronary disease is made difficult by the unpredictability of events in any individual case. Studies of the course of the disease have been attempted by many investigators. While the results have not always shown close agreement, they have nevertheless given us figures that enable one to predict with some approach to accuracy, the percentages of complications and the mean expectation of life for large groups of cases. However, to predict what will happen to one patient is sheer guesswork. Everyone familiar with this disease knows that some of the patients desperately ill with acute coronary occlusion not only survive but eventually make a remarkably good recovery and live for many years. Conversely a patient with an apparently mild seizure may die or if he recovers, remain a cardiac cripple as long as he lives. The patient in whom the disease has progressed only to the

point where it can be recognized, may rapidly grow worse or the disease may remain no more than a slight handicap to him for many years. Even those with findings which indicate that coronary disease has gone far enough to produce extensive changes in the myocardium, may have no symptoms whatever and remain active indefinitely.

Even though at present we have no accurate idea as to how much the things we do prolong the lives of our patients with coronary disease or retard the progress of their disease, one need not feel pessimistic about advances along these lines in the future. We have already learned that the problems are not simple and that they cannot be solved by crude investigative methods. Whether or not we discover the vital link or links in the causation of atherosclerosis, there is little doubt that "closely reasoned argument" and "precise recording" can solve some of the problems of treatment. However, in spite of what has been said above, we can do many things to make the lives of our patients more comfortable and useful and we can protect them to some extent at least from unnecessary disabling illness or sacrifice of their lives.

In this day of specialization it is not uncommon to find a patient under treatment by specialists in various fields independently of each other, reminding one of Stephen Leacock's hero who jumped on his horse and rode off in every direction. In group medicine this evil is avoided to some extent at least by a coördinator. In the ordinary practice of medicine it is the general practitioner who should be the coördinator in cases complex enough to require study by others. Patients should be educated to come to him rather than seek out specialists to examine them for what they think is wrong. He is the one who should decide whether special studies are necessary and also to whom the patient should be sent. Treatment unless of a type requiring special skill or equipment or both should be carried out under his direction.

To use an old medical cliché and say that the treatment of coronary disease must be individualized is almost an understatement. This rule applies to almost everything we try to do for these patients. The passion for standardization of all things that can be standardized has led to certain practices in the treatment of coronary disease that can scarcely be defended on rational grounds. One of these is the dictum that every patient who has had an acute coronary seizure should spend four to six weeks at complete bed rest. We owe a debt of gratitude to those who have led the recent revolt against unnecessarily prolonged

bed rest. Not the least of their accomplishments is to help free physicians from bondage to rules, violation of which has made them subject to criticism for any one of the unpredictable events that may occur at any time in patients with advanced coronary disease. No one at this time knows enough about coronary disease to make dogmatic statements about the grade and duration of rest that would prove best for each patient.

The mental and emotional aspects of coronary disease should never be lost sight of in treatment. The publicity accorded this disease and its manifestations in the lay press, the constant emphasis placed on the possibility of sudden death and the fact that almost everyone has personal knowledge of cases in which sudden death or permanent invalidism has occurred, have engendered fear of coronary disease in those who think they may have it that is apt to complicate treatment. All physicians of experience in this field have seen patients incapacitated from fancied heart disease who have recovered as soon as they were actually convinced that they did not have it. We are inclined to pay more attention to the psychiatric state of those who exhibit their neurosis in plain sight. We may however neglect the mental and emotional reactions of those who do not place them on parade but which nevertheless may have a definite bearing on their symptoms.

One of the most interesting aspects of the influence of mental and emotional factors on the symptomatology of coronary disease may be seen in those who hold total and permanent disability insurance policies. Even after seizures that would be classified on the basis of objective evidence as slight, the prognosis for recovery sufficient to enable them to return to work seems to be far worse than in the case of non-policy holders. The physician who helps his already apprehensive patients increase their fears incurs the risk of prolonging incapacity. It is only the incurable optimists who think nothing can happen to them and therefore fail to coöperate in treatment who are benefitted by stimulating respect for their disease.

Advice to a patient as to rest and activities which fails to take into account his psychology because of concentration on the purely physical aspects of the condition may not turn out as well as one anticipates. The physician should be prepared to compromise between the two and make further adjustments depending on the course of events. In general it has seemed to me far better to permit the victims of coronary disease

to carry on useful even though somewhat restricted lives and even permit recreations that do not tax their hearts too much than to have them slowly disintegrate both physically and mentally in an easy chair. I venture this assertion fully cognizant of the fact that occasionally patients subject to angina pectoris may develop an attack on exertion which instead of subsiding, continues with the development of acute coronary occlusion and myocardial infarction.

Inter-Relationships With Other Diseases

The attempt to correlate all of a patient's symptoms under a single diagnosis has long been regarded as sound in principle. It has not, however, so far as I am aware, been sufficiently emphasized that this principle applies with most force to acute illnesses. In diseases as chronic as coronary disease we have to recognize the fact that some of the symptoms of which a patient complains may arise from another of the various disorders to which human flesh is heir. We have also to consider the influence of each of these disorders on the symptoms of the other. I shall mention only a few of these inter-relationships which seem to me important from the viewpoint of treatment although a fairly extensive list might be prepared. The fact that anemia or hyperthyroidism may aggravate or even precipitate the anginal syndrome or heart failure in patients with coronary disease is well known. Under these circumstances the most effective treatment of the cardiac symptoms is control of the anemia or hyperthyroidism. Pains referred along the brachial plexus or intercostal nerves from non-cardiac causes in cases with coronary disease with or without the anginal syndrome, are apt to cause mental anguish to a patient. If he knows he has heart disease it is difficult to convince him that most of the pains around his heart and down his left arm are not caused by his heart disease. The interrelations of symptoms of gall bladder disease and heart disease are often difficult and sometimes impossible to unravel completely. It may be a nice question to decide whether the gall bladder should be removed. In my experience the anginal syndrome has been relieved in only a relatively small percentage of patients with co-existing gall bladder disease. Thus, in considering operation one must give weight to the added risk because of heart disease and should not have too much confidence that the cardiac symptoms will be improved, although symptoms due to digestive tract disturbance which may simulate anginal pain may be completely relieved.

Perhaps the most confusing of all situations arises when painful esophageal spasm occurs in patients who are also subject to the anginal syndrome because the location and type of distress in the two conditions may be similar. Such a case was reported by Edeiken[6] and we have seen several since that time. Misinterpretation of painful episodes of esophageal spasm as manifestations of coronary disease may intensify the agitation at least partly responsible for their production and make treatment futile.

Emphasis on the principles of treatment of coronary disease discussed above is tantamount to an admission that more direct methods of attacking it are limited in their effectiveness. If we learned how to reverse or even to check the atherosclerotic process, methods of doing so would become the most important thing to talk about.

Diet

Many workers feel that atherosclerosis is essentially the result of a metabolic fault and some go so far as to point to cholesterol as the cause of the trouble, particularly the excessive intake of cholesterol of animal origin. Data obtained from animal experiments and an array of clinical observations can be used to support this view. If or when convincing evidence can be presented that low intake of animal cholesterol prevents the occurrence of coronary atherosclerosis or retards its further development, I believe we will be able to convince some of our patients to eat foods with low animal cholesterol content. We would not even have to bother much about women unless they were already hypertensive or diabetic because of the relative immunity of the remainder to coronary disease. It should be a far easier matter to obtain the coöperation of patients in limiting cholesterol intake than in the painful process of reducing their caloric intake enough to lose weight. It would therefore be difficult to overestimate the importance of proving just what part cholesterol or anything else we ingest plays in the development of atherosclerosis. Everyone who has had experience in necropsy work in China agrees that atherosclerosis is rarely found in the aortas or coronary arteries of the Chinese. It might eventually save thousands of American lives every year, including members of the armed forces if lend lease funds could be allocated to feed enough Chinese over a long enough period of time, diets high in animal cholesterol content such as many Americans use from choice in order to find out

whether their metabolism is superior to ours or whether they are merely more sensible about what they eat. Possibly also careful studies during the next few years in Europe on those whose intake of animal cholesterol has been low almost from the beginning of the present war will yield information of value. It would be most instructive to find out whether those who emphasize the value of such foods as milk, butter and eggs to growing children are laying the foundations for coronary atherosclerosis and are thus unwittingly responsible for premature death in the future of up to 25 per cent of the children whose parents are persuaded to use the diets recommended. If coronary disease is actually more common in the United States than it was a few generations ago it is by no means improbable that changes in diet are at least to some extent at fault, and perhaps not those changes which are most criticized. We must have these questions answered: (1) Is coronary disease caused by a fault in metabolism? (2) Is it caused by excessive intake of cholesterol? (3) Is it caused by a combination of the two factors operating in the same individual? (4) Are none of the above concerned in its production? In formulating diets for patients with the idea of preventing coronary disease, without the answers to these questions we are in the same position as those who solemnly tell us what is good for us to eat. I do not mean to imply that we have not learned much about the use of diet in the treatment of certain diseases nor that the knowledge gained has not been of great value. However, the time has come when we must lift our sights and be concerned with the more remote and therefore less easily discovered effects of special diets. We have already had a good lesson on this subject when it was discovered that the high fat diet for diabetics in pre-insulin days, although it seemed to help the diabetic state at the time, was followed by a much greater incidence of premature atherosclerosis than we now encounter in diabetics. However we do not know what a high fat diet will do to the arteries of non-diabetics.

Physicians have to give advice regarding diet to nearly every patient with coronary disease. If they should be so remiss as to forget it, the patients or their families will almost certainly inquire about it. We all know that these individuals should not overload their stomachs, select foods calculated to test the limits of their digestive capacity, eat a large meal just before going to bed, or starting a golf game, or try to drink all the fluids they can hold because health columnists have said this is a

good thing to do. A marked dietary indiscretion or gastro-intestinal upset may precipitate an attack of acute coronary occlusion in those in whom the stage is set for such a calamity. That the gastro-intestinal tract is liable to become the temperamental prima donna of coronary disease in its more advanced stages is only too well known to everyone who has to treat some of its victims. I have no better explanation for this than anyone else who has discussed it, no new suggestions for diverting patients from concentration on their gastro-intestinal tracts and no additions to propose to the present list of relatively ineffective remedies. It has seemed to me that after other causes of digestive disturbances have been ruled out as completely as possible, psychotherapy with attempts to convince the patient that there is no actual disease of the digestive tract and that his indigestion is the result of disturbance in nervous conrol of that tract may sometimes help more than medication. These patients by abstaining from one food after another in the effort to obtain relief may bring on themselves deficiency states which may actually aggravate their digestive disturbances.

Life insurance statistics have made it clear that obesity after youth carries the penalty of decreased expectation of life. It is not clear, however, whether this is the result of obesity per se or other effects of a possible metabolic fault responsible for obesity despite the fact that those constitutionally slender are apt to regard all obesity as exogenous. There can be little doubt that some of the obese feel better after diet and loss of weight. They are less breathless, gastro-intestnal symptoms may improve and even anginal pains, if they are subject to this disorder, are less easily evoked. Others, however, feel weak and unhappy when placed on a diet. It is not unusual to obtain a history from patients who have been persuaded to lose a lot of weight merely because they were too fat, that loss of weight marked the beginning of illness. Some excessively obese cardiac patients rapidly deteriorate and die of heart failure when placed on drastic reducing diets. Moreover, the frequency of acute coronary occlusion during or shortly after marked loss of weight is such as to raise a question whether this is purely coincidence. While slow weight reduction is doubtless highly beneficial in many, one should probably not try to make all have figures like debutantes.

Medicinal Treatment

Most patients when they visit a physician hope that he will be able

to give them medicine to cure their ills or at least relieve their symptoms. Even though we have not as yet discovered any medicines that will cure coronary disease much can often be accomplished for the relief of symptoms. Moreover, medicinal treatment may be helpful in keeping patients alive following acute coronary occlusion and for the treatment of threatened or actual heart failure. These matters have been discussed at considerable length in textbooks and special articles and I propose to make only a few brief comments upon the practical application of certain forms of treatment.

It would be difficult to find a remedy more effective and less harmful than the nitrites for the relief of an attack of angina pectoris. Nevertheless many patients hesitate to use them except for a severe attack and consequently employ the medication only after the attack has reached its height. It is therefore well to instruct them in detail regarding the use of nitrites and make clear the fact that these remedies are not habit forming, that tolerance increases only slightly and does not persist, and that the drug is more effective if used early in a seizure. On the other hand, many patients who are given nitroglycerin for pains in the chest continue to use it believing it to be helpful when in fact it is not. Its effectiveness can be determined by ascertaining the time relation between placing a rapidly soluble tablet under the tongue and the beginning of relief. If this interval exceeds two or three minutes it is extremely unlikely that the nitroglycerin has anything to do with relief of distress, thus immediately bringing the diagnosis under question. There still seems to be some difference of opinion regarding the relative merits of amyl nitrite and nitroglycerin. The former acts more quickly but its effects are so transient that pain is more likely to recur in a few minutes. Although the dosage is more difficult to control, intelligent patients may become expert in its use, being able to inhale enough to relieve pain and still avoid unpleasant nitrite effects. Many patients prefer nitroglycerin because it can be used without attracting attention. Moreover if it is employed at the very beginning of an attack, it usually acts rapidly enough to prevent severe distress.

One of the questions often asked when a patient's treatment is under discussion is whether orally administered theophylline compounds or papaverine will prove useful. I know of no method by which one can predict their results in any given case. It seems unwise to continue using such remedies over long periods of time without trying to find out

whether they are really beneficial. One can usually obtain evidence on this point in reasonably intelligent patients by alternate periods of administration and withdrawal of the drug under consideration without making other changes in treatment at the same time. There seems little doubt that some patients are helped by such remedies and others not at all. Gastric irritation produced by theophylline or theobromine compounds, although apparently well known by everyone, may be frequently overlooked in practice because symptoms produced by the drug are attributed to the disease. One sometimes obtains greatest success in relieving symptoms merely by withdrawing such medicines.

The indications for the use of digitalis in the treatment of coronary disease are to some extent still a matter of controversy. Coronary disease unless life is terminated by one of the accidents that may occur during acute coronary occlusion such as ventricular fibrillation, rupture of an infarct or embolism, tends to progress slowly or rapidly toward left ventricular failure and its consequences. Experience seems to indicate that digitalis rarely benefits patients with angina pectoris and frequently aggravates this condition. It has some value in helping to prevent attacks of paroxysmal cardiac dyspnea. It is most useful in cases with chronic or established auricular fibrillation to help keep the ventricular rate under control. It is also useful in congestive failure. Digitalis is often administered to patients in advanced stages of coronary disease when rapid deterioration or sudden death are to be looked for. Nevertheless, the frequency of such occurrences at just about the time digitalis effects are obtained suggests that this drug is not without danger and if used even for the more chronic manifestations should be administered cautiously. Experimental studies seem to show that full digitalis dosage increases the mortality of animals with acute coronary obstruction. One may question whether it has any use in human acute coronary occlusion aside from the control of the ventricular rate in such abnormal mechanisms as auricular fibrillation, when there is reason to believe that the rapid rate is contributing to a dangerous grade of heart failure.

In the treatment of acute coronary occlusion the stakes are always death versus an unpredictable grade and duration of recovery. In an illness in which death may occur suddenly without forewarning or the patient who seems almost moribund may recover, one must be cautious in drawing conclusions as to the results of treatment. In deciding on a step in treatment one should give full weight to its dangers as well as

its possible advantages. I have already referred to the possible danger of digitalis. Perhaps no one would deny the value of morphin or drugs with similar actions to relieve pain or restlessness but the last dose which relieves pain completely may produce depression of respiration and perhaps be responsible for the death of the patient. The intravenous injection of theophylline ethylenediamine is often followed promptly by a marked improvement of a profoundly depressed circulation thus averting what had seemed to be almost imminent death. On the other hand, too many patients die within a few minutes after such an injection even though it be given over a period of five to ten minutes, for the death to be always a coincidence. This danger I believe can be almost completely averted by administration of 0.5 gm. of theophylline ethylenediamine diluted with 200 cc. of salt or glucose solution by slow intravenous drip over a period of two hours. It can be repeated several times a day when necessary to sustain the circulation.

The value of oxygen, efficiently administered in high concentration in patients critically ill with acute coronary occlusion is beyond question. However, its use should not be postponed until the patient is critically ill. It often has great value in relieving pain, as can be demonstrated by stopping it temporarily, thus reducing the need for morphin. Moreover it may produce definite improvement in the circulation. Thus, there are reasons for believing that when given promptly it may prevent critical illness or death. The mode of administration is important. Nasal catheters and the masks in popular use are liable to annoy the patient and increase restlessness. A small transparent plastic hood covering only the head and upper chest, such as the one devised by Lambertsen and Godfrey,[7] having the shape of an egg bisected longitudinally and attached to the ordinary air conditioning unit is highly efficient and much more satisfactory from the point of view of the patient and nurse as well as the physician, than any other apparatus I have used including large oxygen tents. Oxygen concentrations of 60 to 88 per cent can be maintained by an oxygen flow of 6 to 10 liters per minute. When the small hood is used, it must be kept under observation in desperately ill patients because of the undesirable concentration of carbon dioxide if the motor stops. It should therefore be removed when the nurse is to leave the room for any length of time.

Surgical Procedures

The idea that some of the problems of circulatory disease can be

attacked by rendering ineffective certain functions of those parts of the nervous system which have to do with the heart and blood vessels although not new, is attracting more and more attention. Procedures designed to block pain impulses have a limited although worthy objective which is to make the patient more comfortable. Among such is the paravertebral alcohol injection procedure developed by Swetlow[8] on the basis of Mandl's observation that angina pectoris can be relieved temporarily by the injection of procain into the same areas and J. C. White's[9] operation of resection of sympathetic dorsal nerve root connections. That these procedures are capable of relieving anginal pains seems to have been established beyond question by competent observers. Personally I have had no experience with White's procedure and little with paravertebral alcohol injection because of the rarity in my experience of cases in which such measures seem necessary for the relief of anginal pain. After one has eliminated hiatus hernia, the varieties of spasm of the gastro-intestinal tract which may accompany gall bladder disease or nervous states, and the various somatic causes of pain in the distribution of the brachial plexus and intercostal nerves in patients who may or may not also have the anginal syndrome, there remain only a few in which nerve block for the relief of the anginal pain itself has seemed to me necessary or even desirable. However, I do not mean to imply that when severe pain, whatever its origin, cannot be relieved by simpler measures, relief should not be sought by nerve block.

It is entirely possible that the extensive sympathectomies now being employed for the treatment of hypertension may retard the development of coronary atherosclerosis in the patients operated on successfully by virtue of a lower blood pressure resulting from the operation. If this proves to be the case, the operation will prolong the lives of those who would otherwise have died as a result of coronary complications of their disease.

The success of sympathectomy in the treatment of peripheral vascular disease seems to depend in large measure on the extent to which vasospasm contributes to the deficiency of blood supply and its relief by operation. Moreover there is now some evidence to indicate that the development of collateral circulation is encouraged by a state of dilatation of vessels already in the neighborhood.[10] If these statements apply to the heart as well as the legs, one of our objectives should be the development of an operation which will produce maximum vasodilatation

of the coronaries and another should be the development of procedures by which the grade of coronary vasospasm can be recognized so that the operation could be applied to suitable cases. By such means it is at least theoretically possible that some of the evil effects of coronary disease could be mitigated.

The Evaluation of New Forms of Treatment

During the course of this discussion, I have repeatedly emphasized the gaps in our knowledge of coronary disease and the limitations of the modes of treatment at our disposal. For such reasons, medicine should be especially careful not to rest on its modest laurels in this field but be eager for new ideas and receptive to new proposals for treatment. However, we have the right to demand that they be based on the closely reasoned argument and precise recording that Sir Thomas Lewis[1] properly insists should characterize medical writings. The criteria upon which the value of a remedy should be based must include sufficient experience with it so that its possible disadvantages or dangers are recognized, accurate diagnosis so that one knows what he is treating and enough precisely recorded data so that the fallacy of post hoc, ergo propter hoc can be excluded. Without such requirements, we shall doubtless continue to have new forms of treatment recommended without adequate study, received by the uncritical with a wave of enthusiasm and then dropped when their lack of value is finally established. With insistence on scientific standards, we shall undoubtedly work our way forward, even though it be at times a slow and tedious process.

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USE OF CONCENTRATED HUMAN SERUM γ-GLOBULIN IN THE PREVENTION AND ATTENUATION OF MEASLES*[1,2,3]

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I. PLASMA FRACTIONATION

1. INTRODUCTION

THE present world conflict has given a tremendous impetus to the practical application of knowledge concerning the blood and its many functional constituents. Whole blood has recently been flown from bleeding centers on our eastern seaboard to the European theatre of operations for use in the treatment of battle casualties within a few days of its collection. Blood plasma, its essential proteins preserved by methods for desiccation from the frozen state worked out in recent years, has been transported all over the world and stored till needed by the men of our armed forces.

Blood is a complex mixture of cells suspended in the plasma and performing many functions, not all of them known. The transfusion of blood has come to be used for the treatment of shock, anemia, infection, agranulocytosis, thrombocytopenic purpura, and the bleeding

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1. Both the clinical studies and the development of the products from blood collected by the American Red Cross have been carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.
2. The studies reported in this paper would not have been possible without the coöperation of a number of agencies and individuals. Most of the work in Boston in 1943 was carried on by Dr. Charles W. Ordman. Field tests of globulin preparations against measles in 1944 have been carried out with the assistance of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, in Philadelphia and Baltimore under the direction of Drs. Joseph Stokes, Jr., Elizabeth P. Maris and Lt. S. S. Gellis, M.C., A.U.S.; in New York City, through the Department of Health, by Drs. Maurice Greenberg, Samuel Frant and David D. Rutstein; in Washington, D. C., under Capt. L. R. Newhouser, M.C., U.S.N. and Dr. Lewis K. Sweet; in Durham, N. C., under Dr. W. C. Davison; and in Boston and vicinity with the coöperation of the Massachusetts Department of Health, the Massachusetts Antitoxin and Vaccine Laboratory and the Health Officers of Arlington, Medford, Malden and Chelsea. We are indebted to the large number of physicians and hospital staff members in various cities who have provided most of the reports on which this study is based; to Dr. William B. Berenberg and the house and resident staff of the Children's Hospital for their assistance in the control and distribution of globulin; and to Miss Virginia Poole, B.A., who has kept the records, tabulated the data and prepared the charts for this report.
3. This paper is No. 32 in the series, "Studies on the Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed in the Department of Physical Chemistry from blood collected by the American Red Cross.

tendency of jaundice and hemophilia, although in only one of these instances, shock due to hemorrhage, are all of its constituents needed to repair the physiological defect. In many of these instances it should be more rational, more effective, and less wasteful to use only that component needed for the particular therapeutic purpose. Thus, the infusion of resuspended red blood cells, as reported by Taylor, Thalhimer and Cooksey[1] and by Cooksey and Horwitz,[2] is a logical use of the chief waste product of plasma production, and raises the hemoglobin level of the anemic patient rapidly without imposing on his circulation the necessity of disposing of the excess plasma. Unfortunately, methods for the separation or preservation of the more labile and less numerous granulocytes and platelets have not been developed.

In the case of plasma, we are dealing with a mixture of many types of protein molecules in a crystalloid solution closely corresponding in composition to the interstitial fluid of the body. The numerous protein constituents of plasma differ in their chemical properties, their source and fate within the body, and the functions which they perform.[3] The isolation of these components in pure form and their chemical characterization has long been an aim of all those interested in human physiology. Military necessity has encouraged the accomplishment of this aim, and has thus opened up new horizons in the treatment and study of disease.

The plasma fractionation program, which originated in a desire to investigate the physiology of the individual plasma proteins, received a tremendous impetus from the need of the armed forces for a compact, safe and effective blood derivative.[4] To meet this need, concentrated human serum albumin was developed and, under Navy contract, has been produced on a large scale from blood collected by the American Red Cross. The methods worked out by Cohn, Oncley, Strong, Hughes and Armstrong[5] for the separation of pooled plasma into a series of fractions, from one of which albumin is prepared, have been devised in such a way as to make available as many as possible of the other functionally important plasma proteins. Thus there have been developed an increasing number of products of plasma fractionation which have useful clinical applications, while the development of others is still in progress.

2. THE PLASMA FRACTIONS

Table I lists the plasma fractions and their derivatives for which

TABLE I

BLOOD AND BLOOD DERIVATIVES

Material	*Fraction*	*Subfraction*	*Functional Component*	*Product*	*Use*
Whole blood			Cells, platelets, plasma		Hemorrhage
Resuspended red cells			Erythrocytes		Anemia
Plasma			Plasma Proteins		Burns, hypoprothrombinemia, hemophilia
Fractions of Pooled Human Plasma	I (Fibrinogen)		Fibrinogen (with thrombin)	Plastics Fibrin films Fibrin foam + thrombin	Dural substitutes Absorbable hemostatic agent Skin grafting
	II + III (α, β, γ -globs.)	II (γ-globs.)	Antibodies (60%)	γ-globin antibodies (Immune serum globulin)	Prophylaxis and therapy of infectious diseases
		III-1 ($\beta + \gamma$-globs.)	Antibodies (40%) Isoagglutinins	Isoagglutinins	Blood grouping
		III-2 (β-globs.)	Prothrombin Complement (C'1)	Thrombin	Hemostatic agent
	IV ($\alpha + \beta$ globs., Lipoproteins)		Hypertensinogen Complement (C'2) Thyrotropin Alkaline phosphatase		
	V (Albumins)		Albumin	Concentrated normal human serum albumin	Shock Edema Hypoproteinemia
	VI (Very little protein. Chiefly salts.)				

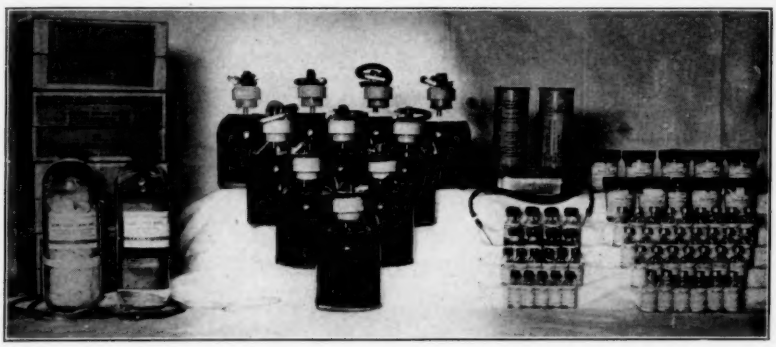

FIGURE 1

THE PRODUCTS WHICH MAY BE OBTAINED FROM THE 10 BLEEDINGS IN THE CENTER

On the left are the five 500 c.c. dried plasma packages (2500 cc.) obtained if all the plasma is used as such. On the right are shown the products of plasma fractionation now obtainable from this amount of blood. These comprise:

1. *Inner row: (top)* 3 packages of albumin (equivalent to 1500 cc. of plasma in osmotic effect); *(middle)* 8 vials of isohemagglutinins (if blood of one group only is used); *(bottom)* 11 vials of globulin antibodies (55 cc.).
2. *Outer row: (top)* 9 packages of fibrin foam; *(bottom)* 30 vials of thrombin.

specific indications have been proved. The availability of these fractions has made possible progress along several lines. First, every donation of blood becomes far more useful if separated into its specific components and used in several different ways (See Fig. 1). Second, it becomes possible to achieve therapeutic results using concentrated and purified proteins for specific purposes, which would be difficult or impossible with whole plasma because of the amounts that would have to be given. Thus, in the treatment of hypoproteinemic edema, a large amount of osmotically active albumin can be administered in a small volume of fluid, without the salt which tends to exaggerate any form of edema. Third, using human plasma fractions as starting material, it is possible to develop entirely new products which can be used for purposes for which plasma is not suitable. Such products are fibrin foam with thrombin and fibrin film, now being used in various surgical procedures. Fourth, with purified proteins available as tools, it becomes possible to investigate many aspects of the physiology of the plasma proteins which are of fundamental importance to an understanding of health and disease.

3. THE PLASMA ALBUMINS

The plasma proteins have been divided by chemists into albumins and globulins. The albumins constitute a relatively homogeneous group of protein molecules which carry the highest net charge and are the most symmetrical, most stable and smallest of the plasma proteins.[3] As a consequence of these chemical characteristics, the albumins exert 80 per cent of the colloid osmotic pressure of the plasma although they constitute less than 60 per cent of the total plasma proteins.[6]

Twenty-five per cent albumin solution, as dispensed in the standard Army and Navy package[7] has approximately the viscosity of whole blood, can be kept for months without refrigeration and can be rapidly injected without reconstitution or preliminary cross matching. A single 100 cc. package containing 25 grams is osmotically equivalent to 500 cc. of citrated plasma but has only 1/6 the bulk or weight of the standard Army-Navy plasma package. The complete safety of albumin and its effectiveness in rapidly restoring a diminished blood volume and thus relieving the symptoms of surgical shock have been amply demonstrated.[8, 9, 10] Once it becomes available to civilians, albumin should be ideal for the physician to carry in his bag or for hospitals to keep on the accident room shelf for the emergency treatment of patients in actual or impending shock.

However, albumin is more than a convenient and effective substitute for plasma; it is a therapeutic agent in its own right with application to certain situations where plasma is ineffective. It supplies a long-felt need in medicine and surgery for a protein solution which can be administered at any desired concentration and with any desired combination of electrolytes. Since albumin is the particular protein in which hypoproteinemic patients are almost always deficient, it is the logical one to administer in the relief of their symptoms. The work of Thorn and his associates[11] in demonstrating that a salt-poor albumin solution will produce diuresis in patients with the nephrotic syndrome is but one example of the many new therapeutic possibilities opened up by this development.

4. THE PLASMA GLOBULINS

The remainder of the plasma proteins are globulins, a group of proteins with diverse chemical characteristics performing many im-

portant functions in the body. These are divided on the basis of their electrophoretic behavior into α, β, γ-globulins and fibrinogen. Blood clotting requires the interaction of two globulins—thrombin, an enzyme which circulates in the form of its inactive precursor, prothrombin, and fibrinogen.[12] From these proteins have been developed fibrin film, used as a dural substitute, and fibrin foam with thrombin, used in surgery, neurosurgery and dentistry as an absorbable hemostatic agent.[13-19] The isohemagglutinins are likewise globulins, and these have been concentrated from bloods of a single specific group for use in the typing of blood for transfusion purposes.[20, 21] In addition, complement, certain hormones and enzymes circulate as, or in close association with, the plasma globulins, although their purification for clinical use has not yet been effected. Finally, we come to those globulins with which we are immediately concerned in this discussion, the antibodies.

Most antibodies are γ-globulins, that is, globulins which migrate most slowly in an electric field, due to their electrical asymmetry and low net charge. Although their net charge is low, the asymmetrical distribution of charges on the molecules of γ-globulin is such that their electric moment is high and their possibilities of interaction with other proteins or smaller molecules very great. The antibodies are quantitatively recovered from the plasma in Fraction II + III, and by the present methods for the further subfractionation of Fraction II & III, about 60 per cent of the antibody activity is recovered in Fraction II and 40 per cent in Fraction III–1. Clinical studies have been carried out with preparations of Fraction II which have been steadily improved until a purity of 95 per cent or better with respect to γ-globulin has been achieved.[22] Methods for the recovery of the remaining 40 per cent of the antibodies in Fraction III–1 are now in process of development.

II. γ-Globulin Antibodies: Laboratory Studies

When the plasma fractionation program was first undertaken, with the separation of the albumin fraction for transfusion purposes, Robinson pointed out the possible practical application of the globulin fraction to the control of infectious diseases. Accordingly, studies were initiated[23] which quickly revealed that the immune bodies present in the plasma pool were quantitatively recovered in Fraction II+III, a crude fraction containing some α—but chiefly β- and γ-globulins, whereas

the other Fractions, I, IV and V, contained a lower concentration of antibody than the original plasma. Under the direction of Dr. A. R. Dochez of the Committee on Medical Research, samples of Fraction II+III were sent to many investigators throughout the country, whose titrations revealed approximately 10-fold concentration over pooled normal human plasma of a large variety of antibodies. These laboratory titrations were supplemented by the clinical tests of Stokes and his colleagues, who demonstrated that preparations of this fraction could be used for the prevention or modification of measles in exposed children.

However, Fraction II+III contains a number of other important functional constituents besides the immune bodies to infectious agents and consequently further subfractionation was carried out, yielding three fractions: III-2, composed chiefly of β-globulin and containing prothrombin, III-1, a mixture of β- and γ-globulins in which the isohemagglutinins are concentrated, and II, comprising chiefly γ-globulin, with marked antibody activity.

Methods for the preparation of Fraction II have been gradually improved so that the γ-globulin content of this fraction, as estimated by electrophoretic analysis, has been increased from roughly 80 per cent to 98 per cent in recent preparations. Enders[24] has carefully measured the concentrations of certain representative antibodies in each preparation of Fraction II for over a year, so that a statistically significant body of data has been accumulated on γ-globulin fractions derived from blood collected in the northeastern, midwestern and Pacific states. This body of data shows considerable uniformity of antibody content despite the collection of blood at different seasons and in widely separated localities. However, it was found last winter that the titer of antibodies to influenza A rose in preparations derived from blood collected after the cessation of an epidemic due to this virus. This is an example of how the preservation of this fraction of pooled normal plasma as a stable dry powder might form an important record of the immune status of a population, thus providing the epidemiologist with a new tool, changes in antibody titers reflecting the sweep of epidemics through the group. Since the pools from which these samples are derived represent from 2,000 to 6,000 donors, the antibody levels should be fairly representative of the immunity of the group rather than of a few exceptional individuals.

TABLE II

TITERS OF REPRESENTATIVE ANTIBODIES

Infection	*Test*	*Fraction II Titer*	*Conc. Factor over normal plasma*	*Convalescent plasma titer*	*Ratio Titer II Conv. plasma*
Typhoid	H. Agglut. O. Agglut.	94 10	20 2	2000 900	1/20 1/90
Influenza A	Comp. Fixation Hirst Test Mouse Prot.	280 308 130	20 10 23	360 500 210	8/10 6/10 2/3
Mumps	Comp. Fixation	98	20	250-1300	1/13-1/4
Diphtheria	Antitoxin (units/cc.)	2.6	25	(.13)	(20)
Scarlet Fever	Antitoxin (units/cc.)	40	22	5-15	2-5
B-Streptococcus	Antistreptolysin (units/cc.)	2500	25	500	5

The antibody titrations carried out under Enders' direction have been used to control the potency of the serum γ-globulin preparations as they have come from the Harvard Pilot Plant and from commercial laboratories operating under contract with the Navy or the American Red Cross. Although considerable variations may occur in these titrations due to inherent difficulties with the tests, all the antibodies followed have been found concentrated from 15 to 30 times in Fraction II. From the chemical standpoint the concentration with respect to γ-globulin is approximately 25-fold. These facts, combined with the association of antibody activity in most hyperimmune animal sera with the γ-globulin fraction and the finding that the antibody titers have not fallen as all but traces of β-globulin have been removed from recent preparations, suggest that most antibodies of normal human blood are γ-globulins.

Although there is a parallel concentration of γ-globulin and antibody in Fraction II, only about 60 per cent of the total antibody activity of Fraction I + II can be accounted for in it. The remaining antibody activity is found in Fraction III-1, which contains both β- and γ-globulins, and studies are now in progress which should make it

possible to recover this moiety for clinical use. One very interesting finding is the behavior of the two typhoid agglutinins. The H or flagellar antigen of the typhoid bacillus is a protein and its agglutinin, like the majority of other antibodies, is concentrated in Fraction II. On the other hand, the O antigen contains a polysaccharide and its agglutinin is concentrated to a marked extent in III-1, as are the isohemagglutinins whose homologous antigens are not protein, but polysaccharide in nature.

Table II indicates the levels of those antibodies which have been carefully followed a sufficient number of times to give an accurate idea of the concentrations to be expected. It will be noted that the concentration factor over normal plasma corresponds closely to the concentration factor for γ-globulin in all but two instances, the typhoid O agglutinin, discussed above, and the Hirst test, in which, for technical reasons, false low readings are obtained. The ratio of the titer of Fraction II to reported values for convalescent plasma gives some idea of those diseases, in which, other factors being equal, γ-globulin might be expected to have some clinical effect. It may readily be seen that γ-globulin approaches the values for convalescent serum in the case of influenza A; it falls far short in typhoid and mumps; while in scarlet fever, and probably diphtheria, it exceeds them.

The process of concentration of the antibody activity of normal human plasma into a single fraction is not only important for the preparation of an effective prophylactic and therapeutic agent, but also for the preservation of this activity for the future. In the process of preparing normal human serum albumin for the armed forces, the plasma from many donors has been subjected to fractionation. This has made available a large amount of human antibody. It has been found that when this is kept properly as dry powder or as the final solution, it is stable for long periods of time. This stability is increased by the use of 0.3 molar (isotonic) glycine as diluent in place of sodium chloride, a change which has been incorporated in the most recent preparations of γ-globulin antibodies. The excellent keeping qualities of human antibodies when concentrated and refined is of great practical importance, since it makes feasible the plan, inaugurated by the American Red Cross with the coöperation of the Navy, for the distribution of γ-globulin in excess of the needs of the armed forces, to the people of the United States through public health agencies.[25]

III. Clinical Use of γ-Globulin Antibodies

1. GENERAL

The use of human blood, plasma, or serum to transfer passive immunity against a number of infections is an established clinical procedure, although the evidence for its effectiveness has not been clear in every case. In some instances normal serum has been used, more frequently convalescent serum, and in the case of pertussis, hyperimmune serum (i.e., the serum of donors already immune whose antibody levels have been further increased by stimulating doses of vaccine). The use of human blood as a source of antibody has the great advantage of freeing the recipient from the dangers and discomforts of the serum disease which so frequently followed the injection of unconcentrated animal sera in earlier days and which still is occasionally seen after administration of the refined and concentrated sera of the present. The difficulty with human antibody preparations in the past has been that their potency has been low, their standardization usually has not been carried out except in the patient, and convalescent sera have often been hard to obtain. Furthermore, the recent evidence incriminating human blood,[26] plasma[27] and serum[28] in the transmission of an agent causing jaundice from donor to recipient has cast some doubt on the relative safety of human as compared to animal serum. The use of γ-globulin obviates many of these objections to the use of human antibody in the form of serum or plasma.

In discussing the use of γ-globulin we shall refer to the injection of antibody before symptoms of disease appear as *prophylaxis,* whether the attempt is to prevent or modify the symptoms, and to the injection of antibody after symptoms have occurred as *treatment.* Two groups of factors will influence the results of passive immunization for either of these purposes. First come the quantitative factors: (a) *the antibody level established in the patient,* which is influenced by the concentration of antibody in the immunizing agent, the size of the dose, the size of the patient, the speed of absorption, and the rate of destruction of antibody in the body; (b) *the antibody level necessary for neutralization* of the toxin, bacterium or virus producing the disease; and (c) *the time of administration of the antibody* in relation to exposure and the length of the incubation period. Second, come the qualitative factors relating to the nature of the infectious agent and the pathogenesis of

the disease. These include its portal of entry, sites of multiplication, incubation period, route of spread, and the stage at which the disease can be recognized. Unfortunately, in the case of measles, the disease for which the efficacy of γ-globulin as a prophylactic agent has been unquestionably proved, quantitative data can only be obtained in humans exposed to the disease, since no laboratory test for antibody to this virus has yet been found.

2. THE USE OF γ-GLOBULIN IN THE PROPHYLAXIS AND TREATMENT OF SPECIFIC INFECTIONS

A. *Measles*

(a) *Historical background:* Measles is a disease for which human blood provides the only known source of antibody. Attempts to produce a satisfactory vaccine for human immunization have not met with success, and therefore it still remains one of those diseases which everyone must have sooner or later. Unlike many virus diseases, the process of acquiring immunity to measles is almost invariably associated with the development of the clinical picture of the disease, although considerable variation in its severity may occur. Immunity to measles is present in the first few months of life provided the mother is immune to this disease. In the transition from the immunity of infancy to the extreme susceptibility of early childhood, there is a period when measles may assume rather mild and atypical forms, presumably because the child has the very low levels of antibody required to attenuate the effect of the virus.

The use of human blood or its derivatives for the prophylaxis of measles has become a standard pediatric procedure. Two alternatives are open to the physician: first, to prevent the disease completely, or second, to attenuate the disease to such an extent that it becomes a relatively minor infection. It is desirable to prevent all symptoms of the disease in sick or debilitated children, in infants between 6 months and 3 years, and in children who must travel or who are on hospital wards where they will expose other sick children. In producing attenuation, the physician is really performing serovaccination, using passive immunization in such a way that the child acquires an active immunity. This is a satisfactory method of active immunization except for the fact that it can only be used when the patient is known to have been exposed to the disease. Two fundamental premises underlie the pro-

cedure: (1) that a mild attack of measles is less dangerous than a severe attack, and (2) that a mild attack of measles produces a lasting immunity. We believe that results achieved with γ-globulin and convalescent serum justify the first premise. To our knowledge, no satisfactory large scale follow-up studies have ever been made which would yield convincing evidence upon the second. However, it is rational to believe that modified measles confers on most individuals a relatively permanent immunity, since spontaneous mild cases of the disease appear to confer protection for life, and there is a general impression that most children who have modified measles do not develop subsequent attacks.

Various sources of human measles antibody have been employed in the past. Whole blood has often been used inadvertently in hospitals. We have recently seen a very mild case of measles occurring seven days after a transfusion in a patient on our own wards. Convalescent serum is, unfortunately, somewhat difficult to obtain in adequate amounts and convalescent serum, or particularly normal adult serum, must be given in rather large doses to be effective. Consequently the discovery by McKhann and his associates[29] that it was possible to extract from human placentas antibody against most of the infections to which the average adult is immune provided a readily available preparation for the prevention and modification of measles which has found widespread use. It seems probable that the placenta itself does not manufacture antibodies but merely allows them to pass from the maternal to the fetal circulation and therefore is a good source of measles antibody because it contains a large amount of blood. The chief difficulty with placental extracts (marketed under the name of Immune Globulin) has been the relatively high incidence of reactions following their use. Their potency in general has not been sufficient to afford complete protection in most cases, although they have been fairly satisfactory for attenuation of measles. These disadvantages have been recently demonstrated in a comparison of γ-globulin with placental extract, made in New York City by Greenberg, Frant and Rutstein.[30]

(b) *Use of γ-globulin in prophylaxis of measles.* (1) *Results.* Stokes, Maris and Gellis[31] first demonstrated the effectiveness of γ-globulin in the prophylaxis of measles, and their result were confirmed by Ordman, Jennings and Janeway.[32] Subsequently, with the coöperation of a large number of physicians in various parts of the country it has been possible to amass a large number of cases for statistical study. These have proved

TABLE III

COMPARISON OF RESULTS OF PASSIVE IMMUNIZATION AGAINST MEASLES WITH VARIOUS AGENTS (UNSELECTED CASES)

Immunizing Agent	*Total # Cases*	*% No Measles*	*% Mild Measles*	*% Average Measles*
Convalescent Serum[1]	1627	75	17	8
Normal Adult Serum[1]	584	56	24	20
Placental Extract[1]	2740	64	31	5
γ-Globulin Antibodies	2738	73	24	3

1. From McKhann (29)

beyond question that γ-globulin provides the physician with the most effective agent for the prevention and modification of measles that is available. The data can be presented best in a series of tables. Table III gives comparative data for various preparations which have been used for this purpose in the past and for γ-globulin, as judged from the over-all results in a large series of unselected cases. Since these figures include all ages and all degrees of exposure, their significance is open to some question. In Table IV will be found the figures for γ-globulin and convalescent serum in comparable groups of children under 12 years of age, intimately exposed within the home. The expected attack rates for the groups are given, as determined by the excellent painstaking studies of Stillerman and Thalhimer[33] in New York City for several years and by Ordman[32] in 1943 in Boston. It can be seen that the results with convalescent serum are as good as with γ-globulin, but the doses necessary are larger.[34]

2. *Dosage.* A physician using an agent such as γ-globulin would like to feel sure that he could achieve complete protection for his patient or satisfactory modification of the disease at will. Unfortunately, he is dealing with a biological system in which the two biggest variables, the susceptibility of the patient and the virulence of the virus, are beyond his control, so he must be content with some failures. In order to obtain complete protection, it is axiomatic that he should give as big a dose as possible as soon after exposure as possible. To modify the disease, he may either delay his injection until it is too late in the incubation period to prevent the disease or he may use a smaller dose

TABLE IV

RESULTS OF PASSIVE IMMUNIZATION AGAINST MEASLES WITH γ-GLOBULIN ANTIBODIES AND CONVALESCENT SERUM

(Selected Cases; Home Exposure; Age Under 12)

	Total # Cases	*% No Measles*	*% Mild Measles*	*% Average Measles*
Attack Rate[1]	34	20	4	76
Attack Rate (0-14 yrs.)[2]	266	25	75	
γ-Globulin Antibodies (6 mos.—12 yrs.) (Dose: 0.5-5 cc.)	1570	65	32	3
Convalescent Serum (6 mos.—15 yrs.) (Dose: 5-20 cc.)[3]	502	50	49*	1

1. Ordman (32)
2. Stillerman and Thalhimer (33)
3. Stillerman, Marks and Thalhimer (34)

* 27 per cent so greatly modified that without close observation 77 per cent might have been classed as having no measles. 4 per cent slightly modified, cases which we probably should have classified as average measles.

of globulin. Which will give the most reliable results? An analysis of our data for the selected group of cases indicates that the physician has a greater chance of producing attenuation or complete suppression of measles, according to his desire, by varying the dose of globulin than by varying the time of its administration. This is clearly shown by the figures in Tables V and VI. Ordinarily measles in the primary case is not recognized until the third or fourth day after onset, when rash or Koplik's spots appear. If, at this point, the physician administers a suitable dose of globulin, he has about a 3 out of 4 chance of accomplishing his aim. Suitable doses appear to be as follows:

For protection (first 6 days after exposure): 0.08-0.1 cc./lb.
For modification (first 8 days): 0.02-0.025 cc./lb.
(When administered later in the incubation period, the dose should be increased.)

Greenberg, Frant and Rutstein[30] in a study of γ-globulin suggested by Dr. William Thalhimer and carried out by the Health Department of New York City have shown that, using a standard 2 cc. dose of globulin

TABLE V

RELATION OF TIME OF INJECTION OF γ-GLOUBULIN TO RESULTS
(1024 Cases; all doses)

Time after exposure	*% No Measles*	*% Mild Measles*	*% Average Measles*
0—2 days	64	35.2	0.8
3—5 days	66.8	32.2	1
6—8 days	51.6	42.7	5.7

TABLE VI

RELATION OF DOSE OF γ-GLOBULIN TO RESULTS
(1024 Cases; first 8 days)

Dose (cc./lb.)	*% No Measles*	*% Mild Measles*	*% Average Measles*
.01 —.0375	33	63.1	3.9
.0375—.075	55.2	40.6	4.2
.075 —.2	83.7	15.5	0.8

and a standard time of injection, the degree of protection varies inversely with the age of the patient. This confirms the validity of calculating dosage on a weight basis.

3. *Duration of immunity*. Undoubtedly, the duration of immunity will bear a direct relation to the size of the dose given and to the condition of the patient. For example, a patient with nephrosis might lose the antibody rapidly in the urine, or a patient with high fever might be expected to destroy it more rapidly than normal. In our experience a protective dose gives complete protection for 2-3 weeks in a normal child and should be repeated after 3 weeks if complete protection is still desired in the face of a new exposure.

4. *Safety*. The globulin is administered intramuscularly, in the buttocks if a fairly large dose is given. In ordinary doses with a good needle, the injection is practically painless. The incidence of reactions in a large series of cases has been exceedingly low, and most of these have been very mild local reactions (Table VII). Care should be taken

TABLE VII

REACTIONS ON INJECTION OF γ-GLOBULIN

Type of Reaction	*Number*	*Per Cent*
Local	17	0.6
Febrile	12	0.4
General*	6	0.2

2738 injections: 35 reactions; 1.2%

* Headache: 1; Dizziness: 1; Loose stools for 48 hrs. after injection: 2; Orbital edema: 1.

to check that the needle does not enter the vein, since the standard preparation is not suitable for intravenous use.

One of the important clinical syndromes which has recently been recognized is that of homologous serum or inoculation jaundice.[35] This disease, which may or may not be caused by a virus identical with that of epidemic hepatitis (catarrhal jaundice), occurs after an incubation period of 3 to 6 months following the injection of occasional lots of human serum or plasma derived from small pools. Presumably the infective agent circulates for some time in the blood of patients who subsequently come down with typical symptoms of epidemic hepatitis. It has sufficient resistance to withstand inactivation at 56° C. for an hour, the process of desiccation from the frozen state, and fairly long periods of storage in the ice box. We have naturally been very much concerned about the possibility of transmitting this virus by the injection of γ-globulin. The statistical chances of this seemed somewhat greater than with convalescent serum because the pools of plasma were derived from several thousand donors. For this reason we have made follow-up studies from 3 to 6 months after injection in as many instances as possible. Out of 294 individuals so followed after the season of 1942-43, only one case of jaundice was observed; this occurred 3 months after injection and probably was pure coincidence since 73 other children who received this preparation did not develop jaundice. During the past season, 1943-44, we were able to follow up 869 individuals, none of whom has developed jaundice.

5. *Modified measles.* The disease which results when an attenuating

TABLE VIII

COMPLICATIONS OF MEASLES IN CHILDREN UNDER 12 RECEIVING γ-GLOBULIN

(1570 cases, 497 cases of mild measles, 54 cases of average measles)

Age	*Dose cc./lb.*	*Days from exposure to injection*	*Result*	*Complications*
2 yrs.	.02	9	Severe measles	Staphylococcus aureus pneumonia and empyema with recovery
11 mos.	.025	6	Average measles	Mild encephalitis with recovery
2 yrs.*	.025	—	Average measles	Otitis media, simple
4½ yrs.	.017	6	Mild measles	Otitis media, simple
4 yrs.	.023	5	Mild measles	Otitis media, simple

* Child had reaction with chills, fever and edema of eyelids day after injection of globulin.

3 complications in 54 cases of average measles: incidence = 5.5%
2 complications in 497 cases of mild measles: incidence = 0.4%

dose of globulin is given at the proper time after exposure may vary from a barely recognizable illness lasting a day, with very slight fever and a faint sparse rash, to one which is but little milder than the ordinary case of measles. In general, the malaise, prostration, and catarrhal symptoms are little in evidence, and fever and rash are the only signs of infection, but any combination of symptoms may occur. The incubation period is somewhat prolonged at times, perhaps because the disease is not recognized until the rash appears, but the duration of symptoms is rarely over two or three days. A number of patients have been observed in whom mild catarrhal symptoms without rash occurred at the proper time after exposure and were presumably due to the disease. Other patients who have received globulin have developed a few pinkish macules, particularly over the upper trunk, from 12 to 18 days after exposure, as the only sign of infection.

Complications appear to be infrequent with modified measles. Stillerman, Marks and Thalhimer[34] observed complications in 1.0 per cent of 502 children given convalescent serum for measles prophylaxis. In a boys' school where globulin was administered to half of the remaining

TABLE IX

USE OF γ-GLOBULIN TO CONTROL OUTBREAKS OF MEASLES ON PEDIATRIC WARDS

	No. Outbreaks	*No. Children*	*Not Followed*	*No Measles*	*Mild Measles*	*Average Measles*
Number	39	395	95	286	13	1
Per cent	—	—	—	95.3	4.3	0.4

susceptible boys during a severe measles epidemic, there were five cases of otitis media and two cases of sinusitis in a group of fifteen uninoculated boys with measles and only one mild case of otitis media in an equal number of immunized boys who contracted the disease.[32] In the series of cases reported to us by various physicians the incidence of complications has been approximately ten times as high in the small group among whom globulin failed to modify the disease as in the large group among whom the disease was attenuated (Table VIII).

6. *Control of measles in pediatric wards.* Outbreaks of contagious disease are a source of frequent difficulty in the administration of pediatric wards and institutions for children. The availability, safety and reliability of γ-globulin makes it particularly valuable for the control of such outbreaks. γ-globulin has been administered to children exposed in 39 outbreaks of measles in hospital wards. Table IX gives the results. These have been so good that when a case of measles occurs on our wards, we now only isolate the primary case and give a protective dose to the remaining susceptible children. Thereafter, any non-immune children admitted to the ward in the next 3 weeks should probably be immunized, but in practice we have immunized the newcomers only if mild measles develops in any of the original group.

c. *γ-globulin in the treatment of measles.* Measles differs from many virus diseases in that its course can be influenced by antibody even after clinical symptoms have begun. Stokes, Maris and Gellis[31] were able to modify the course of the disease in a number of instances if they administered large doses of γ-globulin (15-30 cc.) after the onset of the catarrhal stage but before the rash appeared. Stokes[36] has pointed out that, in the absence of chemotherapeutic agents for virus diseases,

the possibility of treating many of them with antibody still exists, provided the disease can be recognized sufficiently early.

B. OTHER DISEASES

There are a number of other infectious diseases for which it is conceivable that γ-globulin might provide a possible means of prophylaxis or therapy. *Chicken pox* is, if anything, a greater nuisance than measles on pediatric wards, but it is doubtful from the incomplete evidence yet available whether γ-globulin provides an answer to this problem. Although a fair titer of *mumps* complement-fixing antibody is present, Stokes and Enders[37] showed that in 10 cc. doses, γ-globulin would not protect susceptible children against this infection. As yet, no clinical studies of the utilization of the antibody against *influenza A* have been undertaken.

The fact that γ-globulin contains scarlatinal antitoxin in 2-5 times the concentration of most pools of scarlet fever convalescent serum has led to clinical trials of its effectiveness in the treatment of *scarlet fever*. These studies are incomplete as yet, but there is reason to believe that concentrated γ-globulin may prove of value in both the therapy and prevention of scarlet fever.

IV. SUMMARY

1. Concentrated human serum γ-globulin derived from blood collected by the American Red Cross contains a 25-fold concentration of most of the antibodies present in normal adult serum. This makes it possible to give the equivalent of 125 cc. of pooled adult serum in a single intramuscular injection of 5 cc.

2. This material is now being distributed by the American Red Cross, through Public Health agencies, for the prevention and modification of measles, a purpose for which it has been proved particularly effective and safe.

3. When administered in the first six days after exposure to measles, a dose of 0.08-0.1 cc. per pound will give protection to roughly three out of four individuals, with mild measles in the fourth, while a dose of one-quarter this much, or 0.02-0.025 cc. per pound will result in an attack of mild measles in most cases.

4. In a large series of cases, very few reactions to intramuscular injection of the globulin have been observed, and these have been mild

and chiefly local.

5. The complication rate in modified measles appears to be definitely lower than in the typical disease.

6. Studies are in progress to discover other clinical uses for this convenient form of concentrated human antibody.

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